Exhibit 3

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Attachment 2

PHYSICIAN'S RESOURCE MANUAL ON OSTEOPOROSIS

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Introduction

Osteoporosis is a condition in which bone tissue is reduced in amount, increasing the likelihood of fracture Although fractures of the spine, hip, and wrist are most typical, fractures of other bones, such as the ribs, humerus, and pelvis, are not uncommon In 1985, there were 247,000 hip fractures in the United States, 8% of women who are now 35 years old will experience a hip fracture in later life The one-year excess mortality of hip fracture is 12% to 20% In 1986, the annual cost of osteoporosis was 7 to 10 billion dollars Osteoporosis represents a major public health problem

Two categories of osteoporosis have been identified primary and secondary Primary osteoporosis is by far the most common form of the condition and includes postmenopausal osteoporosis (Type I), aging-associated osteoporosis (Type II), previously termed senile osteoporosis, affecting a majority of individuals over the age of 70 to 80 years, and idiopathic osteoporosis, a disorder of unknown cause that affects premenopausal women and men who are middle-aged or younger In secondary osteoporosis, an identifiable agent or disease process causes loss of bone tissue Included are inflammatory disorders, disorders of bone marrow cellularity, and disorders of endocrine control of bone remodeling

Osteoporosis reflects the inadequate accumulation of bone tissue during growth and maturation, excessive losses thereafter, or both Since residual bone density at age 60 to 90 years is the net result of these factors, and since there are no safe, effective ways to rebuild the osteoporotic skeleton, prevention, in terms of maximizing maturational gains in bone density and minimizing postmaturity losses, emerges as the crucial strategy Consequently, a knowledge of preventive approaches is essential, one must be aware of the efficacy and safety of estrogen and progestin therapy, intake of calcium and other nutrients, exercise, calcitonin, diphosphonates, and other modalities on the horizon Prevention also requires an understanding of predictive factors, so that the likelihood of osteoporosis may be judged, and an awareness of methods for estimating bone density

In managing the care of patients with established osteoporosis, it is necessary to exclude potentially treatable secondary osteoporosis to protect the patient against further bone loss, to invoke measures that can reduce the likelihood of injury and fracture, and to pave the way for treatments that might be available in the future, some of which are now being tested

The purpose of this guide is to help the clinician prevent, diagnose, and treat osteoporosis In addition, we have included the latest information about osteoporosis as presented at the 1987 workshop on osteoporosis, cosponsored by the National Institutes of Health and the National Osteoporosis Foundation

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The Biology of Bone

The skeleton serves to support the body, protect vital organs, anchor muscles, and store homeostatically active minerals—principally calcium Bones vary in structure according to their specific functions While 80% of all bone is compact (cortical), as in the skull, the remaining 20% is cancellous (spongy, trabecular), as predominates in the vertebrae Bone tissue consists of two phases an organic matrix containing collagen, various noncollagen proteins, and proteoglycans, and a mineral phase, mainly hydroxyapatite In addition to collagen, matrix proteins of special biologic interest are osteocalcin (also called bone GLA protein because it contains gamma-carboxyglutamic acid residues), which is a calcium-binding, vitamin K-dependent protein (like clotting factors), osteonectin, which has a high affinity for hydroxyapatite and collagen, and phosphoproteins These proteins may be involved in the process of mineralization and/or mineral stabilization Bone is also enriched with several stimulators of bone-cell proliferation, and differentiation-promoting proteins that may expedite fracture repair and bone remodeling

Bone Remodeling

All bone undergoes continuous turnover throughout life, although compact bone does so more slowly than cancellous Turnover is engineered by a process of remodeling, which permits the repair of skeletal microdamage and provides a mechanism for the release of calcium into the circulation to satisfy homeostatic demands In remodeling, teams of well-differentiated bone cells, termed remodeling units, combine to resorb a microscopic quantum of bone tissue and then repair the resorption-mediated defect

The Remodeling Cycle

A local remodeling cycle (Figure 1) begins with activation, a change in the local milieu that attracts osteoclasts—multinucleated bone-resorbing cells—to the bone surface Evidence indicates that activation occurs when remodeling stimuli (hormones, physical forces) locally alter the behavior of dormant cells that line bone surfaces, thus exposing underlying bone surfaces that contain chemical attractants for the osteoclasts Osteoclasts, currently thought to originate by fusion of bone marrow mononuclear cells, then migrate to the newly exposed surfaces, attach by a specialized fimbriated organelle (ruffled membrane) and proceed to resorb bone mineral and organic matrix via the release of acid and proteolytic enzymes Following completion of a resorption cavity (Howship's lacuna), alkaline phosphatase-rich bone-forming osteoblasts of bone-marrow mesenchymal-cell-origin infiltrate the area, line the freshly resorbed surface, and synthesize calcifiable organic matrix Some osteoblasts are internalized in the newly elaborated matrix, destined to become osteocytes Osteocytes maintain contact with each other and with surface osteoblasts via cell processes that reside in the microcanalicular system of bone This system provides an enormous surface area of cell-bone contact for mineral exchange An entire remodeling cycle, from activation to complete repair, takes about 100 days At any one time, about two million remodeling units are active throughout the human skeleton

Remodeling almost exclusively takes place in the internal (cortical, endosteal, trabecular) bone surfaces and intracortical loci (haversian remodeling), periosteal surfaces do not remodel vigorously, except at sites of tendon insertion

The resorptive and formative phases of remodeling are linked or "coupled" in three ways First, they appear in close and obligatory sequence De novo bone formation, bypassing activation, occurs on periosteal surfaces (appositional bone growth) but not normally on the endosteum Second, the quality of bone is preserved, the new bone is normally as good (or as bad, in conditions such as

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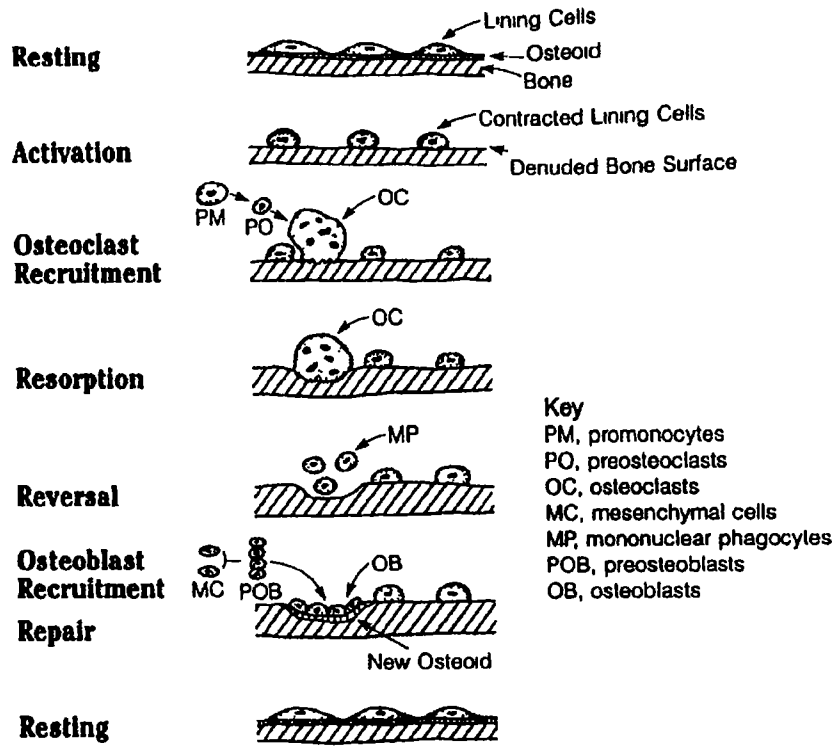

Figure 1 The remodeling cycle Resting bone surfaces are converted to remodeling surfaces via a process of activation—exposing bone surface molecules which are chemotactic for osteoclasts Activation is at least a two-step process—contraction of lining cells and enzymatic removal of surface osteoid Osteoclasts, derived from bone marrow monocyte precursors, attach and resorb bone Mononuclear phagocytes, perhaps involved in resorption and/or in signalling the onset of formation, inhabit resorption bays during the "reversal" phase Osteoblasts are then recruited to repair the resorption cavity

osteogenesis imperfecta) as the old Third, the amount of bone is preserved, at least in the short term Repair of resorption defects is virtually complete

Influential Factors in Bone Remodeling

Bone remodeling is controlled by various systemic hormones and local factors Activators of bone remodeling, and hence of resorption, include parathyroid hormone (PTH), prostaglandins of the "E" series, $1\alpha,25-(OH)_2$ vitamin D (the active metabolite of vitamin D), and thyroid hormone Monokines (regulatory proteins of monocytic origin) and lymphokines (regulatory proteins of lymphocytic origin) have also been shown to influence bone remodeling Interleukin 1, a

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peptide derived from macrophages and other cell types and best known as a promoter of lymphocyte growth, also stimulates bone resorption By contrast, interferons inhibit bone resorption Other inhibitors of resorption are calcitonin, estrogens, and perhaps other sex steroids Agents that enhance osteoblast activity and stimulate bone growth include the bone-derived growth factors, insulin, the somatomedins, prostaglandins in low concentrations, and perhaps testosterone and progesterone In addition to activating resorption, $1\alpha,25-(OH)_2$ vitamin D, recognized as an essential factor in promoting intestinal calcium absorption, may also exert a direct anabolic effect on osteoblasts There is evidence that physical deformation, perhaps by changing local surface electrical charges and promoting local prostaglandin production, can stimulate bone-forming cells Various types of electrical stimulation are applied to bones in order to promote fracture healing Glucocorticoids at pharmacologic doses inhibit osteoblast activity

Approximately 99% of total body calcium is deposited in bone, a small amount is distributed between the extracellular fluid and intracellular compartments Calcium exists as a free ion, which is homeostatically active, and in association with protein—principally albumin—and with low-molecular-weight organic acids A complex hormonal regulatory system, acting in part via regulation of bone remodeling, serves to maintain a normal blood ionized calcium concentration Decreases in blood calcium, which can result from reduced intake, reduced intestinal absorption, enhanced urinary loss, or sequestration (eg, at sites of fat necrosis), elicit PTH secretion, which, in turn, promotes bone resorption and the renal tubular reabsorption of calcium In addition, PTH enhances the activity of renal 1α-hydroxylase, the enzyme responsible for mediating the conversion of 25-hydroxyvitamin D to $1\alpha,25-(OH)_2$ vitamin D This culminates in enhanced intestinal calcium absorption Normalization of blood calcium suppresses PTH secretion By contrast, secretion of the osteoclast inhibitor calcitonin is stimulated by increases in blood ionic calcium—as might be achieved by ingestion of a calcium load Vitamin D is in reality a hormone, for it is synthesized from 7-dehydrocholesterol by skin cells during exposure to ultraviolet light, and undergoes a two-step activation process (25-hydroxylation in the liver and 1α-hydroxylation in the kidney) to $1\alpha,25-(OH)_2$ vitamin D before it can become biologically active Furthermore, its activation is controlled, PTH phosphate, and perhaps calcium and other factors regulate 1α-hydroxylase

Progression of Changes in Bone Density

Bone density and its closely related property, bone strength, change considerably throughout life Density increases during the growth period and continues to rise even after growth in height stops, peaking at age 25 to 30 years for predominantly trabecular bone (vertebrae) and 35 to 40 years for predominantly cortical bone (femur) After skeletal maturity is reached, bone loss begins and persists until age 85 to 90 years Lifetime losses range from 20% to 30% for males and up to 45% or 50% for some females These changes are attributable to a remodeling imbalance, which, though minute at each remodeling locus, is nevertheless cumulative and generalized throughout the entire skeleton. Overall, postmaturity losses amount to 25% to 1% per year, women experience an acceleration of bone loss to as much as 2% to 3% per year, which begins in the perimenopausal period and continues for 5 to 10 years after menopause This acceleration, accompanied by a high rate of bone turnover, stems from the menopausal decline in estrogen production and perhaps in the production of other hormones such as progesterone Rates of trabecular bone loss exceed those of cortical bone loss after menopause

It is evident that decreases in bone density associated with aging, postmenopausal acceleration of bone loss, and the susceptibility of remodeling to homeostatic demands combine to influence the amount of bone tissue at any one time and determine the prospect for excessive bone loss, osteoporosis

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Not surprisingly, risk factors for fractures and osteoporosis are reflective of these phenomena Also evident is the fact that certain strategies for preventing osteoporosis, such as the use of estrogen therapy in postmenopausal women, are designed to compensate for physiologic mechanisms underlying enhancement of bone loss (eg, estrogen deficiency) Expanded knowledge of bone biology is yielding new information concerning potential markers of bone remodeling (eg, the measurement of serum osteocalcin) and also new strategies for therapy (eg, the potential use of bone growth factors)

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